REMARKS

Applicants have herein amended the first paragraph of the specification to correct the priority claim. Applicants have updated the status of U.S. Application No. 09/318,208. In addition, it has come to the attention of the undersigned that benefit to co-pending U.S. Application No. 09/373,658 and additional applications in the priority chain were not listed in the specification. Thus, Applicants have attached to this amendment a petition to accept unintentionally delayed benefit under 37 C.F.R. §§ 1.78(a)(3) and (6) along with authorization to charge the surcharge under § 1.17(t) to our deposit account. Contingent upon granting of this petition, Applicants respectfully request that the first paragraph of the specification be amended as described above.

Applicants have herein amended claim 1 to correct a minor typographical error (*i.e.*, misspelling of the word "Syndrome" as "Syndrom"). Applicants particularly note that the present amendment of claim 1 is not intended to narrow, nor does it narrow, the scope of the claimed subject matter.

No new matter has been added. Applicants submit that the claims 1-3, 5-7 and 9-32, as pending upon entry of this amendment, are in condition for allowance.

I. Claim Rejections under 35 U.S.C. § 112, first paragraph

A. Written Description of Claims 1-3, 5-7 and 9-32

Claims 1-3, 5-7 and 9-32 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, it was asserted:

> Claims 1, 2, 5 and 6 have been amended to incorporated the limitation "wherein said polypeptide is capable of inhibiting angiogenesis" in order to comply with the written description requirement. However, the added subject matter is not supported by the original disclosure. As stated in the previous rejection, amino acids 214-439 contain the metalloprotease domain of METH2; amino acids 440-529 contain the disintegrin domain of METH2; amino acids 530-583 contain a first TSP-like domain of METH2; and amino acids 837-890 contain the second TSP-like domain of METH2. The specification states on page 5, lines 3-4 that peptide[s] and recombinant proteins derived from the TSP-like domain of METH1 and

> METH2 blocked VEGF-induce[d] angiogenesis. This does not provide support for polypeptides which minimally comprise amino acid residues outside of the TSP-like domains having the characteristic of being capable of inhibiting angiogenesis, such as residues 214-239 [should be 439] and 440-529.

See, Paper No: 20060309, page 2, item 5.

Applicants respectfully disagree and traverse. The original disclosure, as filed, fully supports claims 1-3, 5-7 and 9-32. The specification at page 5, lines 3-4 simply describes the results of experiments shown in Figure 6. The description for Figure 6 as provided on page 5, lines 3-20, indicates that each METH1 and METH2 peptide tested showed inhibition of angiogenesis in the assay. Thus, this provides full support for use of the longer METH1 and METH2 proteins and for peptides derived from the Type I repeats of METH1 and METH2 for inhibition of angiogenesis. However, additional disclosure in the specification provides full support for claims 1-3, 5-7 and 9-32 as they apply to peptides "which minimally comprise amino acid residues outside of the TSP-like domains." In particular, the specification at page 354, line 5 through page 355, line 11 specifically discloses METH1 and METH2 polypeptides "which may be used to inhibit angiogenesis" including, "amino acids 214 to 439", "amino acids 440 to 529", "amino acids 280 to 606", and "amino acids 529 to 548" of METH2 (SEQ ID NO:4). It is also disclosed that METH2 proteins lacking any or all TSP domains may be used to inhibit angiogenesis.

Accordingly, the specification provides explicit, full support for use of each of the peptides covered by claims 1-3, 5-7 and 9-32 for inhibition of angiogenesis. Further, the specification provides full support for use of METH1 and METH2 peptides "lacking TSP3, TSP2, and TSP3" domains (i.e. lacking all TSP domains) for inhibition of angiogenesis (*See* page 355, lines 5-7). Finally, Applicants point out that pre- and post-filing publications support the use of integrin antagonists (including polypeptides with disintegrin domains) for inhibition of angiogenesis. For example, Brooks, et al. discuss that $\alpha v\beta 3$ (i.e. integrin) antagonists have been shown to block angiogenesis in vivo (Brooks, Stromblad et al. 1996, See page 690, 1st column, penultimate paragraph). Further, Senger, et al. used integrin-specific antibodies to block VEGF-induced angiogenesis (Senger, Claffey et al. 1997, See Abstract). Finally, a number of references demonstrate that disintegrin-domain containing polypeptides inhibit angiogenesis (Yeh, Peng et al. 1998; Kang, Lee et al. 1999; Markland, Shieh et al. 2001; Yeh,

Peng et al. 2001). Hence, the claims currently pending are fully supported by an adequate written description sufficient to fulfill the requirements of 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully request that the rejection of claims 1-3, 5-7 and 9-32 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

B. Enablement of Claims 1-3, 5-7 and 9-32

Claims 1-3, 5-7 and 9-32 were also rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing "to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." More particularly it was asserted that the specification "provides an experimental model system for the demonstration of anti-angiogenic activity." But, the specification "does not provide objective evidence of the treatment" of individuals suffering from angiogenesis-mediated diseases nor does it "provide objective evidence that the administration of the claimed polypeptides could function as a birth control treatment."

It appears that the Examiner holds the instant specification non-enabling due to an alleged lack of empirical evidence demonstrating successful treatment of individuals suffering from angiogenesis-mediated diseases and due to an alleged lack of empirical evidence demonstrating successful birth control by administration to patients. The Applicants respectfully disagree and traverse.

The present specification discloses novel anti-angiogenic proteins related to thrombospondin and discloses that these novel proteins contain metalloproteinase domains, disintegrin domains and TSP-like domains (*See* page 2, paragraph 1 and page 102, lines 11-23). The present specification also discloses that these proteins demonstrate anti-angiogenic activity in assays for the same (*See* Example 4 on page 391, line 21 through 394, line 27 and Figure 6). The sequences of these polypeptides are fully described (*See* SEQ ID NOs:1-4, Figures 1 and 2, and page 134, line 21 through page 275, line 3). In addition, methods for making these polypeptides, variants and fragments thereof are fully disclosed (*See* page 119, line 13 through page 134, line 20). Further, methods for assaying for anti-angiogenic activity are fully described using art-accepted "gold standard" assays for angiogenesis and inhibitors of angiogenesis (Brem 1999, *See* page 5, last paragraph and Specification, Example 4 and Figure 6). The specification provides significant guidance regarding anti-angiogenic activity and use in treating a variety of

angiogenesis-mediated diseases (*See* page 341, line 9 through page 348, line 11). In particular, the specification discusses the use of the peptides of the invention in providing birth control (*See* page 345, lines 13-18). The specification also provides significant guidance on the formulation of pharmaceutical compositions containing the polypeptides of the invention, administration modalities, and dose ranges to achieve the desired therapeutic effect (*See* page 355, line 25 through page 356, line 10; page 372, line 9 through 376, line 25; and Example 26). Thus, Applicants respectfully submit that the specification provides a disclosure that fully enables the scope of claims directed to treatment of angiogenesis-mediated diseases using METH1, METH2 and variants thereof. Finally, the level of skill in the art is sufficiently high that, given the guidance in the specification, only routine experimentation would be needed to practice the claimed treatment methods in a variety of angiogenesis-mediated diseases.

Applicants point out that "it is not necessary that a patent applicant test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one of skill in the art to carry out the invention commensurate with the scope of his claims." *Chugai*, 927 F.2d at 1213 (citing *Angstadt*, 537 F.2d at 502)(emphasis added). In addition, Applicants note that empirical data is not a threshold requirement for sufficient enabling disclosure. Instead, it has been found that "a patent specification is required to contain a disclosure, either through illustrative examples or written description, that is sufficient to teach one skilled in the art how to make and use the invention as broadly as it is claimed. *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)(emphasis added). This point was further clarified by the court which held that "[t]he first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant". *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971)(emphasis added).

According to the court, "[a]s a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (emphasis added). Further, the court has found that "it is incumbent upon the Patent Office, whenever a

rejection [for lack of enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." Cf. *In re Gazave*, 54 CCPA 1524, 379 F.2d 973, 154 USPQ 92 (1967); *In re Chilowsky*, 43 CCPA 775, 229 F.2d 457, 108 USPQ 321 (1956).

The Applicants respectfully submit that the Examiner has not met this burden. The Examiner has not provided any reason to doubt the supporting disclosure in the specification, nor has any "acceptable evidence or reasoning which is inconsistent with the contested statement" been provided. The Examiner has only asserted that "demonstration that the instant peptides inhibits angiogenesis in the models used in the specification does not provide enablement for the treatment" of the angiogenesis-mediated diseases "because there is 'no teachings on the amounts of peptides required...the duration of treatment necessary...the concentration of peptides necessary, and the length of exposure...necessary" for treatment of the diseases and conditions claimed. The Examiner further states that "there are not teachings regarding the plasma concentration, tissue localization or the appropriate timing and duration of the treatment necessary to function in birth control."

The Applicants respectfully remind the examiner that, according to The U.S.P.T.O. Guide, "Training Materials For Examining Patent Applications With Respect To 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications" (available online at http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm):

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. Section 112, is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); and *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643
>
> (CCPA 1965); see also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
>
> It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be

> able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. Section 112.

As discussed above, the specification provides significant guidance on the formulation of pharmaceutical compositions containing the polypeptides of the invention, administration modalities, and dose ranges to achieve the desired therapeutic effect. One skilled in the art, given the guidance provided in the specification and the considerable knowledge in the art regarding effective dosages for polypeptide-based therapeutics, would need only routine experimentation to practice the treatment methods covered by the pending claims.

Finally, the Examiner cites Johnson and Tracey to support the assertion that there are "general problems with the administration of peptide and protein drugs, namely short half-life in vivo, necessitating multiple administrations." The Examiner further claims that the "art teaches that ["]major stability, release and manufacturing challenges" (page 81[7], second column, lines 1-5) must be met in order to overcome the technical difficulties associated with the delivery of peptides in vivo, because of the necessity of supplying repeated or sustained dosages over time necessary to overcome the short half-life in vivo." Finally, the Examiner concludes that:

> The art teaches that considerations in formulating the delivery of repeated or sustained dosages of peptides are stabilization of the peptides from degradation in vivo, and stabilization of peptides during the manufacturing process, and the subsequent controlled release of said stabilized peptides in vivo in the appropriate quantities. The specification does not teach a means for the delivery of these small peptides to all the disease sites encompassed by all the angiogenesis-mediated diseases claimed, such that the level of peptide is maintained for the time required to produce efficacy against said angiogenesis-mediated diseases, or to inhibition [sic] tumor growth or tumor metastasis in a patient, in order to function as a birth control agent. Therefore it would be undue experimentation in order for one of skill in the art to determine a means for the delivery of the peptides to the tumor in a patient in such quantities which would be efficacious to said patient, wherein said delivery means would include how to stabilize the peptides from degradation in vivo, or during the manufacturing process, and how to release the stabilized peptides in vivo in the appropriate quantities.

See, Paper No. 20060309, page 3-5, item 6.

Applicants respectfully disagree and traverse. Contrary to the Examiner's assertion, the article by Johnson and Tracey does not discuss technological barriers to the successful application of polypeptide-based therapeutics. Instead, the article is focused on the development of novel delivery products, such as polymeric delivery systems, for therapeutic proteins and peptides (*See* page 817, 1st column, last sentence to top of 2nd column). Further the "major stability, release, and manufacturing challenges" discussed by Johnson and Tracey are for "developing delivery products for proteins and peptides," such as polymeric delivery systems, and are not challenges that "must be met in order to overcome the technical difficulties associated with the delivery of peptides" as was asserted by the Examiner. Johnson and Tracey focus on "polymeric delivery systems" and stress the broad applicability of their analysis to a "variety of peptide and drug delivery systems" (*See* page 817, 2nd column, 1st paragraph).

Applicants respectfully submit, in contrast to the Examiner's assertion, that polypeptide-based therapeutics have and continue to be successfully applied in the clinic. For Example, Rathin C. Das reports that as of 2000, approximately 60 protein therapeutics had been approved by the FDA with another ~200 under development (Das 2000). In 2004, Pavlou and Reichert report that 73 protein-based therapeutics had reached the market with greater than 80 in development (Pavlou and Reichert 2004).

Finally, in contrast to the Examiner's assertions, Applicants respectfully point out that the specification provides significant guidance as to "means for the delivery of these small peptides to all the disease sites encompassed by all the angiogenesis-mediated diseases claimed." For example, on page 355, line 25 through page 356, line 10, the specification provides guidance on pharmaceutically effective dose ranges, parental delivery methods (e.g. subcutaneous infusion using a mini-pump), and acceptable routes of administration. Further, the specification provides significant guidance regarding formulations, delivery systems, and routes of administration on page 372, line 9 through page 376, line 25. Finally, in Example 26, the specification details considerations regarding pharmaceutically-effective dose ranges, routes of administration, various delivery/release systems, formulations, concentrations, and contemplated combination therapies.

Applicants respectfully submit, as discussed above, that a disclosure in compliance with the written description requirement of the first paragraph of § 112 must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. Further, the "how to use" prong

of the enablement requirement of 35 U.S.C. § 112, first paragraph is satisfied if a person of ordinary skill in the art would have reasonably believed an applicants' asserted utility. Applicants submit that a person of ordinary skill in the art would have reasonably believed the Applicants' asserted utility given:

1) the disclosure in the present specification of novel anti-angiogenic proteins related to thrombospondin and the disclosure that these novel proteins contain metalloproteinase domains, disintegrin domains and TSP-like domains; (*See* page 2, paragraph 1 and page 102, lines 11-23)
2) the disclosure in the present specification that these proteins demonstrate anti-angiogenic activity in assays for the same; (*See* Example 4 on page 391, line 21 through 394, line 27 and Figure 6)
3) the knowledge that prior to Applicants' earliest filing date, that the TSP domain of thrombospondin was effective to inhibit angiogenesis; and
4) the disclosure in the present specification that, "[a]ngiogenesis is a key step in the metastasis of cancer (Folkman, *Nature Med. 1*:27-31 (1995)) and in abnormal wound healing, inflammation, rheumatoid arthritis, psoriasis, and diabetic retinopathy, it is integral to the pathology (Folkman *et al.*, *Science 235*:442-447 (1987)), engendering the hope that these pathological entities could be regulated by pharmacological and/or genetic suppression of blood vessel growth (Iruela-Arispe *et al.*, *Thromb. Haem. 78*:672-677 [(]1997))." (*See* page 2, paragraph 2)

One of skill in the art need only read the Applicants' specification for guidance on how to make METH1, METH2, fragments of METH1 and METH2, and variant proteins; guidance on how to test for anti-angiogenic activity; and for guidance on formulation and administration in a clinical setting in order to make and use the invention within the scope of the claims.

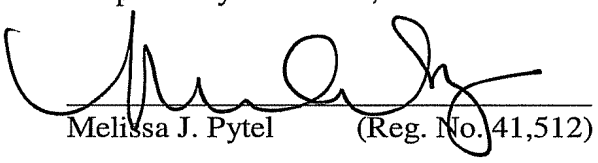
Thus, Applicants submit that the claimed therapeutic methods are fully enabled in view of the high degree of skill in the art pertaining to the use of polypeptide-based therapeutics and the teachings of the instant application regarding METH1 and METH2 therapeutic methods. Accordingly, Applicants respectfully request that the rejection of claims 1-3, 5-7 and 9-32 under 35 U.S.C. § 112, first paragraph, enablement, be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request that the remarks of the present response be entered and made of record in the present application. If any additional information is needed, Applicants respectfully request that the Examiner contact the undersigned to facilitate prosecution. The application is believed to be in condition for allowance and early notice to that effect is earnestly solicited. If a fee is required in connection with this paper, please charge Deposit Account No. 08-3425 for the appropriate amount.

Respectfully submitted,

Date: September 8, 2006



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